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(54) Title: ORAL 2-METHYL-THIENO-BENZODIAZEPINE FORMULATION

(57) Abstract

The invention provides a pharmaceutically elegant solid oral formulation of olanzapine and a process for making such formulation.

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ORAL 2-METHYL-THIENO-BENZODIAZEPINE FORMULATION

This invention provides an improved pharmaceutically elegant tablet formulation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, hereinafter referred to as olanzapine, and processes for the preparation thereof.

Olanzapine has shown great promise in the treatment of psychotic patients and is currently being evaluated for that purpose. Certain tablet formulations of olanzapine are known, as described in U.S. Patent No. 5,229,382. However, improved oral formulations were desired in light of the moisture sensitive, metastable nature of olanzapine, the tendency of olanzapine to undesirably discolor in the known tablet formulation, and due to the surprisingly potent nature of olanzapine.

The presently claimed invention provides a pharmaceutically elegant solid oral formulation for comprising olanzapine intimately mixed with a bulking agent, binder, disintegrant, a dry binder to provide friability, and a lubricant; wherein such solid oral formulation is coated with polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose.

It is particularly preferred that the polymer coat does not contain polyethylene glycol.

Further, the invention provides a method for preparing pharmaceutically elegant, stable solid oral olanzapine formulations having a polymer coat selected from the group consisting of hydroxypropyl methyl cellulose,

hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose, comprised of using a high shear aqueous wet granulation with fluid bed drying process.

Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.

Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.

Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.

Applicants have discovered that coating the solid oral formulation with a polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon

in the formulation. The formulation is most preferredly in a tablet form; however, granule formulation and the like are desired as well.

Most preferred polymer coats are hydroxypropyl methyl cellulose, hydroxypropylcellulose, methylcellulose, and ethylcellulose. An especially preferred polymer coat is hydroxypropyl methylcellulose.

It is especially preferred that the formulation contain the most stable anhydrous form of olanzapine, referred to herein as Form II; however, other forms of olanzapine are contemplated. Form II has a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48

d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper Kα radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

The formulation of the invention preferredly contains substantially pure Form II as the active ingredient.

As used herein "substantially pure" refers to Form II associated with less than about 5% undesired polymorphic form of olanzapine (herein referred to as "Undesired Form"), preferably less than about 2% Undesired Form, and more preferably less than about 1% Undesired Form. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II preferably contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content

of acetonitrile. Additionally, Form II preferredly contain less than 0.5% of associated water.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

Form II is the most stable anhydrous form of olanzapine known and is therefore important for the commercial development of pharmaceutically elegant formulations. Olanzapine may form an undesired crystal form in the presence of certain solvents and excipients, therefore, in making the compositions of the invention it is most desired to prepare the formulation using a method which does not require dissolution of the olanzapine substance. The desired Form II can be converted to less desirable polymorphic forms by contact with methylene chloride, for example. Additionally, for example, polyethylene glycol contact with the olanzapine substance produces undesired discoloration, particularly under moist conditions.

Applicants believe that a dry blend direct compression process or dry granulated processes for preparing solid oral formulations create a greater chance that poor dose uniformity will occur. In light of the potent nature of olanzapine, consistent dose uniformity is imperitive. In accordance with this invention, Applicants have discovered that a high shear aqueous wet granulation with fluid bed drying is the most effective method for preparing pharmaceutically elegant, stable, oral olanzapine formulations.

Uncoated tablets stored at ambient conditions (approximately 23°C and 40% relative humidity) in amber, high density polyethylene bottles do not show signs of discoloration after 24 months; however, if the bottle is

opened such that the tablets are exposed to open air ambient conditions then discoloration occurs within 5 days.

A new solid oral formulation was prepared that used a hydroxypropropyl methylcellulose subcoating and a white color coating. The new formulation did not discolor after 90 days of open dish storage at 40°C, 60°C, 40°C/75 %RH, ambient temperature with 75% RH, or at ambient temperature with 85% RH. The hydroxypropyl methylcellulose coating which is free of polyethylene glycol is much preferred to ensure that discoloration does not occur on the tablet surface. It provides an effective barrier between the white color coat which provides an acceptable medium for imprinting and color dressing of the product. The hydroxypropylmethylcellulose coating provides sufficient barrier to prevent discoloration attributable to the polyethylene glycol in the white color coat. Alternative white film coat formulas containing alternative plasticizers were evaluated; however, none were able to prevent discoloration in all test conditions after 90 days of storage. Therefore, the hydroxypropyl methylcellulose coat or subcoating is a surprising and important component of pharmaceutically elegant solid oral formulations of olanzapine.

A diluent or bulking agent should be selected to provide an increase in tablet size. The artisan can utilize known methods to select a bulking agent which provides hardness, friability, and disintegration time that is satisfactory for pharmaceutical usage. The bulking agent should be selected to provide a tablet that has characterstics desired by the patient as well as comply with applicable regulatory guidelines.

One especially preferred diluent or bulking agent is lactose. Various forms of lactose are appropriate for such formulations including anhydrous, hydrous, and spray dried forms. The most desired form of lactose can be selected based on desired dissolution, content uniformity, hardness, friability, and disintegration time. The skilled

artisan is aware of the regulatory requirements for hardness, friability, and disintegration time and can adjust the diluent or bulking agents using known techniques to achieve the desired physical characteristics.

The formulation should include a binder for use in the granulation step. The artisan can choose an appropriate binder based on the acceptable viscosity, and desired hydration. Hydroxypropyl cellulose is especially preferred for use as a binder in the granulation step. The hydroxypropyl cellulose may vary in particle size. Fine grade hydroxypropyl cellulose is especially preferred for most claimed formulations.

The desired formulation includes a disintegrant for use in the granulation as well as in the running powders to facilitate the disintegration process. There are a variety of grades available, and the grade may be selected based on the acceptable batch variability. A particularly prefered disintegrant is crospovidone. A fine grade of crospovidone provides particularly desirable consistency between batches.

The artisan may choose appropriate dry binders using known methods. Such binders should be selected to assure that satisfactory friability is attained. Most preferably, dry binder is microcrystalline cellulose; however, other appropriate dry binders may be selected. Such microcrystalline cellulose may be in a granular form.

The artisan can choose an appropriate lubricant to prevent sticking and picking of the tablets to the compression tooling. One preferred lubricant is magnesium stearate.

The artisan can readily choose other appropriate aqueous dispersion film coats (color mix) for application over the hydroxypropyl methylcellulose layer. Typically, the color mixture is a dry blend of ingredients which may be dispersed in water and used as an aqueous dispersion to film coat solid formulations. One example of a typical color mixture is comprised of hydroxypropyl

methylcellulose, polyethylene glycol, polysorbate 80, and titianium dioxide.

A variety of edible inks known to the artisan are appropriate for imprinting the finished formulation. For example, one typical edible ink is comprised of shellac, ehtyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue.

The solid formulation is most preferably subcoated with hydroxypropyl methylcellulose, coated with a color coat, and imprinted with an edible ink. The solid formulation may be polished using standard methods such as carnauba wax polishing, if desired.

Olanzapine is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. For treatment of central nervous system disorders, a dose range of from 1 to 30 mg, preferably 1 to 20 mg per day is suitable. Radiolabelled Form II 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine, can be detected in the saliva and thus the compound can potentially be monitored in patients to assess compliance.

A preferred formulation of the invention is a solid oral formulation comprising from about 1 to about 20 mg olanzapine as an active ingedient, wherein such solid oral formulation is coated with hydroxypropyl methylcellulose. Especially preferred is an oral formulation comprising from 1 to 20 mg of anhydrous Form II olanzapine as an effective amount of the active ingredient, provided that such solid oral formulation is coated with hydroxypropyl methylcellulose.

Most preferably, the solid oral formulation is contained in packaging materials which protect the formulation from moisture and light. For example, suitable

packaging materials include amber colored high density polyethylene bottles, amber colored glass bottles, and other containers made of a material which inhibits the passage of light. Most preferably, the packaging will include a desiccant pack. The container may be sealed with an aluminum foil blister to provide the desired protection and maintain product stability.

A study of the hydroxypropyl methylcellulose sub-coated tablets in an amber colored bottle having a desiccant pack stored at harsh, 40°C/75% RH conditions for six months showed pharmaceutically acceptable stability with a 0.4 % to about 1.2% increase in total related substances.

The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. Olanzapine can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. It is most desirable to prepare a rapidly dissolving formulation comprising substantially pure crystalline Form II. Such substantially pure crystalline Form II olanzapine may be prepared using the techniques described herein by the Preparation section herein *infra*.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

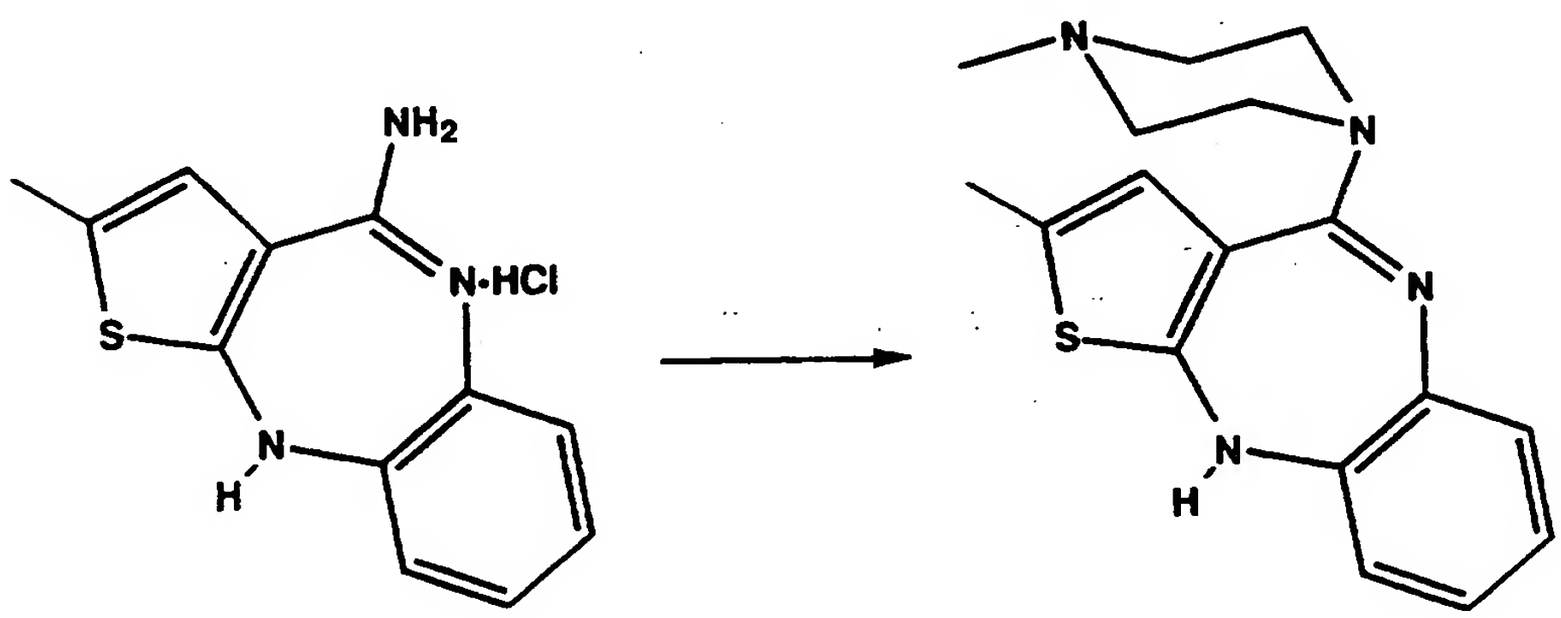
The formulations were studied to assure that the Form II polymorph was substantially pure using ^{13}C Cross polarization / magic angle spinning (CP/MAS) NMR. Spectra were obtained using a Varian Unity 400 MHz spectrometer operating at a carbon frequency of 100.577 MHz and equipped with a complete solids accessory and Varian 5 mm or 7 mm VT CP/MAS probes. Measurement conditions were optimized for Olanzapine Form II and were as follows: 90° proton r.f. pulse 4.5 ms, contact time 1.1 ms, pulse repetition time 5 s, MAS frequency 7.0 kHz, spectral width 50 kHz, and acquisition

time 50 ms. Chemical shifts were referenced to the CH_3 of hexamethylbenzene (d = 17.3 ppm) by sample replacement. It was determined that the substantially pure Form II polymorph is retained throughout the formulation process claimed herein. Therefore, the formulations of this invention provide substantially pure Form II olanzapine polymorph in a pharmaceutically elegant formulation without producing undesired polymorphic transformation.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	:	6 volumes
Intermediate 1	:	75 g
N-Methylpiperazine (reagent)	:	6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until ≤ 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency ≥ 97%, total related substances < 0.5% and an isolated yield of > 73%.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the olanzapine (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension

described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

EXAMPLE 2

The process substantially as described above in Example 1 was repeated using the following ingredients to provide pharmaceutically elegant tablet formulations containing 1, 2.5, 5, 7.5, and 10 mg olanzapine, respectively, per tablet:

1 mg olanzapine per tablet:

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	1.0
Other Ingredients	
Lactose	67.43
Hydroxypropyl Cellulose	3.40
Crospovidone	4.25
Microcrystalline Cellulose	8.50
Magnesium Stearate	0.42
Subcoating	
Hydroxypropyl Methylcellulose	1.70
Coating	
Color Mixture White	3.47
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 2.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	2.5
Other Ingredients	
Lactose	102.15
Hydroxypropyl Cellulose	5.20
Crospovidone	6.50
Microcrystalline Cellulose	13.00
Magnesium Stearate	0.65
Subcoating	
Hydroxypropyl Methylcellulose	2.60
Coating	
Color Mixture White	5.30
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 5.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	5.00
Other Ingredients	
Lactose	156.00
Hydroxypropyl Cellulose	8.00
Crospovidone	10.00
Microcrystalline Cellulose	20.00
Magnesium Stearate	1.00
Subcoating	
Hydroxypropyl Methylcellulose	4.00
Coating	
Color Mixture White	8.16
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 7.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	7.50
Other Ingredients	
Lactose	234.00
Hydroxypropyl Cellulose	12.00
Crospovidone	15.00
Microcrystalline Cellulose	30.00
Magnesium Stearate	1.50
Subcoating	
Hydroxypropyl Methylcellulose	6.00
Coating	
Color Mixture White	12.24
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 10.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	10.00
Other Ingredients	
Lactose	312.00
Hydroxypropyl Cellulose	16.00
Crospovidone	20.00
Microcrystalline Cellulose	40.00
Magnesium Stearate	2.00
Subcoating	
Hydroxypropyl Methylcellulose	8.00
Coating	
Color Mixture White	16.32
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Claims

1. A solid oral formulation comprising olanzapine as an active ingredient intimately mixed with a bulking agent; binder, disintegrant, a dry binder to assure adequate friability, and a lubricant; wherein such solid oral formulation is coated with a polymer selected from the group cosisting of hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose.

2. A formulation as claimed by **Claim 1** wherein the polymer coat is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropylcellulose, methylcellulose, and ethylcellulose

3. A formulation as claimed by **Claim 2** wherein the polymer coat is hydroxypropylmethyl cellulose.

4. A formulation as claimed by any one of Claims 1 to 3 wherein the polymer coat is free of propylene glycol.

5. A formulation as claimed by **Claim 4** wherein the bulking agent is lactose.

6. A formulation as claimed by **Claim 4** wherein the binder is hydroxypropyl cellulose and the disintegrant is crospovidone.

7. A formulation as claimed by any one of Claims 1 to 6 wherein the dry binder is microcrystalline cellulose.

8. A formulation as claimed by any one of Claims 1 to 7 wherein the lubricant is magnesium stearate.

9. A formulation as claimed by any one of Claims 1 to 8 wherein the hydroxypropyl methylcellulose is a subcoating which is further coated with a aqueous dispersion film coat.

10. A formulation as claimed by Claim 9 wherein the solid formulation is imprinted using an edible ink.

11. A formulation as claimed by Claim 9 wherein the formulation comprises from about 1 to about 3 % w/w olanzapine; from about 69.5 to about 87.5 % w/w lactose; from about 3.5 to about 4.5 % w/w hydroxypropyl cellulose; from about 4 to about 6 % w/w crospovidone; from about 9 to about 11 % w/w microcrystalline cellulose; and from about 0.25 to about 1 % magnesium stearate.

12. A formulation as claimed by any one of Claims 1 to 11 wherein the solid formulation is a tablet.

13. A formulation as claimed by Claim 12 wherein each tablet provides a dose of olanzapine selected from the group consisting of 1, 2.5, 5, 7.5, 10, 15, and 20 mg.

14. A formulation as claimed by any one of Claims 1 to 13 wherein olanzapine is substantially pure Form II polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d (A)
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366

3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

15. A process for preparing a stable pharmaceutically elegant solid oral formulation containing olanzapineas an active ingredient and having a polymer coating selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose, comprising high shear aqueous wet granulation with fluid bed drying.

16. A process as claimed by Claim 15 wherein olanzapine is substantially pure Form II polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d (A)
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158

4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

17. A solid formulation as claimed by any one of Claims 1 to 14 for use in treating a condition selected from the group consisting of psychosis, schizophrenia, a schizophriform disorder, mild anxiety, a gastrointestinal disorder, and acute mania.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/03918

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/32, 9/36
US CL :424/464, 474, 475, 479, 480, 482

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 474, 475, 479, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,172,831 A (CHAKRABARTI ET AL.) 30 October 1979, example 37.	1, 12
A	US 5,229,382 A (CHAKRABARTI ET AL.) 20 July 1993, example 4.	1, 12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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(54) Title: ORAL 2-METHYL-THIENO-BENZODIAZEPINE FORMULATION

(57) Abstract

The invention provides a pharmaceutically elegant solid oral formulation of olanzapine and a process for making such formulation.

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ORAL 2-METHYL-THIENO-BENZODIAZEPINE FORMULATION

This invention provides an improved pharmaceutically elegant tablet formulation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, hereinafter referred to as olanzapine, and processes for the preparation thereof.

Olanzapine has shown great promise in the treatment of psychotic patients and is currently being evaluated for that purpose. Certain tablet formulations of olanzapine are known, as described in U.S. Patent No. 5,229,382. However, improved oral formulations were desired in light of the moisture sensitive, metastable nature of olanzapine, the tendency of olanzapine to undesirably discolor in the known tablet formulation, and due to the surprisingly potent nature of olanzapine.

The presently claimed invention provides a pharmaceutically elegant solid oral formulation for comprising olanzapine intimately mixed with a bulking agent, binder, disintegrant, a dry binder to provide friability, and a lubricant; wherein such solid oral formulation is coated with polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose.

It is particularly preferred that the polymer coat does not contain polyethylene glycol.

Further, the invention provides a method for preparing pharmaceutically elegant, stable solid oral olanzapine formulations having a polymer coat selected from the group consisting of hydroxypropyl methyl cellulose,

hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose, comprised of using a high shear aqueous wet granulation with fluid bed drying process.

Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.

Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.

Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.

Applicants have discovered that coating the solid oral formulation with a polymer selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon

in the formulation. The formulation is most preferredly in a tablet form; however, granule formulation and the like are desired as well.

Most preferred polymer coats are hydroxypropyl methyl cellulose, hydroxypropylcellulose, methylcellulose, and ethylcellulose. An especially preferred polymer coat is hydroxypropyl methylcellulose.

It is especially preferred that the formulation contain the most stable anhydrous form of olanzapine, referred to herein as Form II; however, other forms of olanzapine are contemplated. Form II has a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48

d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper $K\alpha$ radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

The formulation of the invention preferredly contains substantially pure Form II as the active ingredient.

As used herein "substantially pure" refers to Form II associated with less than about 5% undesired polymorphic form of olanzapine (herein referred to as "Undesired Form"), preferably less than about 2% Undesired Form, and more preferably less than about 1% Undesired Form. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II preferably contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content

of acetonitrile. Additionally, Form II preferredly contain less than 0.5% of associated water.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

Form II is the most stable anhydrous form of olanzapine known and is therefore important for the commercial development of pharmaceutically elegant formulations. Olanzapine may form an undesired crystal form in the presence of certain solvents and excipients, therefore, in making the compositions of the invention it is most desired to prepare the formulation using a method which does not require dissolution of the olanzapine substance. The desired Form II can be converted to less desirable polymorphic forms by contact with methylene chloride, for example. Additionally, for example, polyethylene glycol contact with the olanzapine substance produces undesired discoloration, particularly under moist conditions.

Applicants believe that a dry blend direct compression process or dry granulated processes for preparing solid oral formulations create a greater chance that poor dose uniformity will occur. In light of the potent nature of olanzapine, consistent dose uniformity is imperitive. In accordance with this invention, Applicants have discovered that a high shear aqueous wet granulation with fluid bed drying is the most effective method for preparing pharmaceutically elegant, stable, oral olanzapine formulations.

Uncoated tablets stored at ambient conditions (approximately 23°C and 40% relative humidity) in amber, high density polyethylene bottles do not show signs of discoloration after 24 months; however, if the bottle is

opened such that the tablets are exposed to open air ambient conditions then discoloration occurs within 5 days.

A new solid oral formulation was prepared that used a hydroxypropropyl methylcellulose subcoating and a white color coating. The new formulation did not discolor after 90 days of open dish storage at 40°C, 60°C, 40°C/75 %RH, ambient temperature with 75% RH, or at ambient temperature with 85% RH. The hydroxypropyl methylcellulose coating which is free of polyethylene glycol is much preferred to ensure that discoloration does not occur on the tablet surface. It provides an effective barrier between the white color coat which provides an acceptable medium for imprinting and color dressing of the product. The hydroxypropylmethylcellulose coating provides sufficient barrier to prevent discoloration attributable to the polyethylene glycol in the white color coat. Alternative white film coat formulas containing alternative plasticizers were evaluated; however, none were able to prevent discoloration in all test conditions after 90 days of storage. Therefore, the hydroxypropyl methylcellulose coat or subcoating is a surprising and important component of pharmaceutically elegant solid oral formulations of olanzapine.

A diluent or bulking agent should be selected to provide an increase in tablet size. The artisan can utilize known methods to select a bulking agent which provides hardness, friability, and disintegration time that is satisfactory for pharmaceutical usage. The bulking agent should be selected to provide a tablet that has characterstics desired by the patient as well as comply with applicable regulatory guidelines.

One especially preferred diluent or bulking agent is lactose. Various forms of lactose are appropriate for such formulations including anhydrous, hydrous, and spray dried forms. The most desired form of lactose can be selected based on desired dissolution, content uniformity, hardness, friability, and disintegration time. The skilled

artisan is aware of the regulatory requirements for hardness, friability, and disintegration time and can adjust the diluent or bulking agents using known techniques to achieve the desired physical characteristics.

The formulation should include a binder for use in the granulation step. The artisan can choose an appropriate binder based on the acceptable viscosity, and desired hydration. Hydroxypropyl cellulose is especially preferred for use as a binder in the granulation step. The hydroxypropyl cellulose may vary in particle size. Fine grade hydroxypropyl cellulose is especially preferred for most claimed formulations.

The desired formulation includes a disintegrant for use in the granulation as well as in the running powders to facilitate the disintegration process. There are a variety of grades available, and the grade may be selected based on the acceptable batch variability. A particularly prefered disintegrant is crospovidone. A fine grade of crospovidone provides particularly desirable consistency between batches.

The artisan may choose appropriate dry binders using known methods. Such binders should be selected to assure that satisfactory friability is attained. Most preferably, dry binder is microcrystalline cellulose; however, other appropriate dry binders may be selected. Such microcrystalline cellulose may be in a granular form.

The artisan can choose an appropriate lubricant to prevent sticking and picking of the tablets to the compression tooling. One preferred lubricant is magnesium stearate.

The artisan can readily choose other appropriate aqueous dispersion film coats (color mix) for application over the hydroxypropyl methylcellulose layer. Typically, the color mixture is a dry blend of ingredients which may be dispersed in water and used as an aqueous dispersion to film coat solid formulations. One example of a typical color mixture is comprised of hydroxypropyl

methylcellulose, polyethylene glycol, polysorbate 80, and titianium dioxide.

A variety of edible inks known to the artisan are appropriate for imprinting the finished formulation. For example, one typical edible ink is comprised of shellac, ehtyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue.

The solid formulation is most preferably subcoated with hydroxypropyl methylcellulose, coated with a color coat, and imprinted with an edible ink. The solid formulation may be polished using standard methods such as carnauba wax polishing, if desired.

Olanzapine is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. For treatment of central nervous system disorders, a dose range of from 1 to 30 mg, preferably 1 to 20 mg per day is suitable. Radiolabelled Form II 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine, can be detected in the saliva and thus the compound can potentially be monitored in patients to assess compliance.

A preferred formulation of the invention is a solid oral formulation comprising from about 1 to about 20 mg olanzapine as an active ingedient, wherein such solid oral formulation is coated with hydroxypropyl methylcellulose. Especially preferred is an oral formulation comprising from 1 to 20 mg of anhydrous Form II olanzapine as an effective amount of the active ingredient, provided that such solid oral formulation is coated with hydroxypropyl methylcellulose.

Most preferably, the solid oral formulation is contained in packaging materials which protect the formulation from moisture and light. For example, suitable

packaging materials include amber colored high density polyethylene bottles, amber colored glass bottles, and other containers made of a material which inhibits the passage of light. Most preferably, the packaging will include a desiccant pack. The container may be sealed with an aluminum foil blister to provide the desired protection and maintain product stability.

A study of the hydroxypropyl methylcellulose sub-coated tablets in an amber colored bottle having a desiccant pack stored at harsh, 40°C/75% RH conditions for six months showed pharmaceutically acceptable stability with a 0.4 % to about 1.2% increase in total related substances.

The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. Olanzapine can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. It is most desirable to prepare a rapidly dissolving formulation comprising substantially pure crystalline Form II. Such substantially pure crystalline Form II olanzapine may be prepared using the techniques described herein by the Preparation section herein *infra*.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

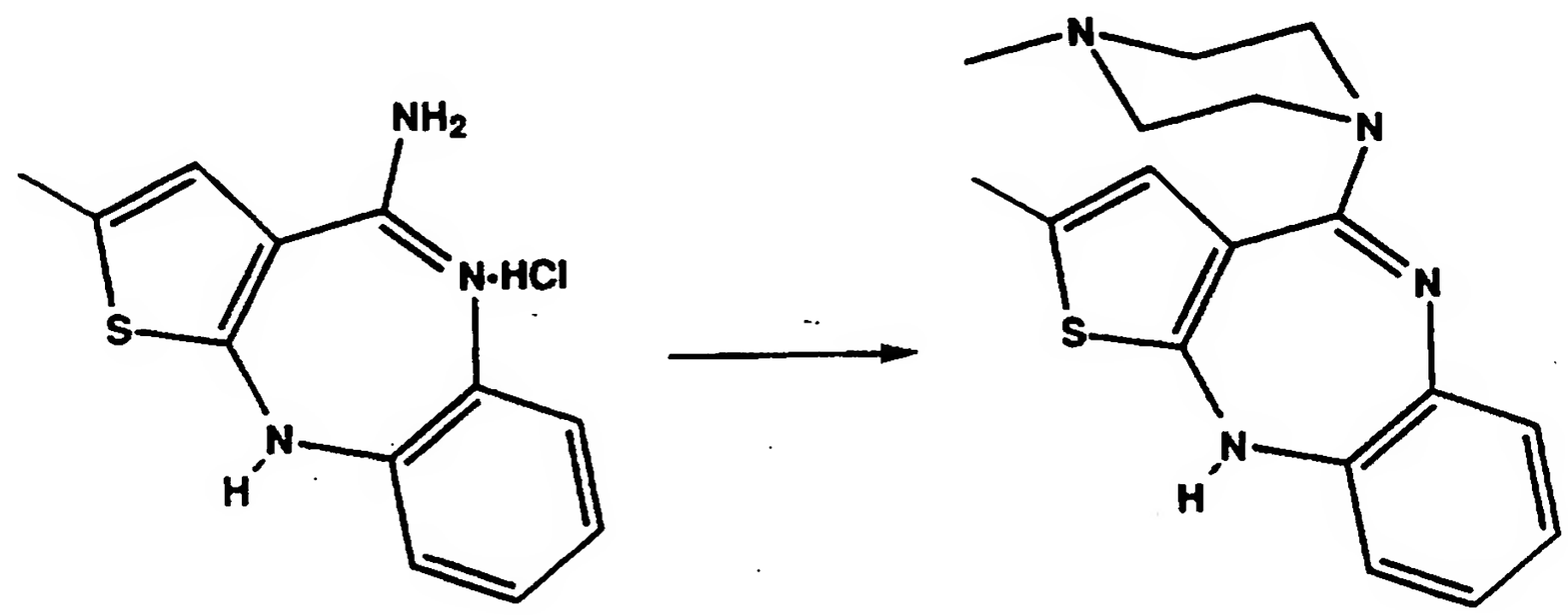
The formulations were studied to assure that the Form II polymorph was substantially pure using ^{13}C Cross polarization / magic angle spinning (CP/MAS) NMR. Spectra were obtained using a Varian Unity 400 MHz spectrometer operating at a carbon frequency of 100.577 MHz and equipped with a complete solids accessory and Varian 5 mm or 7 mm VT CP/MAS probes. Measurement conditions were optimized for Olanzapine Form II and were as follows: 90° proton r.f. pulse 4.5 ms, contact time 1.1 ms, pulse repetition time 5 s, MAS frequency 7.0 kHz, spectral width 50 kHz, and acquisition

time 50 ms. Chemical shifts were referenced to the CH_3 of hexamethylbenzene (d = 17.3 ppm) by sample replacement. It was determined that the substantially pure Form II polymorph is retained throughout the formulation process claimed herein. Therefore, the formulations of this invention provide substantially pure Form II olanzapine polymorph in a pharmaceutically elegant formulation without producing undesired polymorphic transformation.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	:	6 volumes
Intermediate 1	:	75 g
N-Methylpiperazine (reagent)	:	6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until ≤ 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency ≥ 97%, total related substances < 0.5% and an isolated yield of > 73%.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the olanzapine (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension

described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

EXAMPLE 2

The process substantially as described above in Example 1 was repeated using the following ingredients to provide pharmaceutically elegant tablet formulations containing 1, 2.5, 5, 7.5, and 10 mg olanzapine, respectively, per tablet:

1 mg olanzapine per tablet:

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	1.0
Other Ingredients	
Lactose	67.43
Hydroxypropyl Cellulose	3.40
Crospovidone	4.25
Microcrystalline Cellulose	8.50
Magnesium Stearate	0.42
Subcoating	
Hydroxypropyl Methylcellulose	1.70
Coating	
Color Mixture White	3.47
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 2.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	2.5
Other Ingredients	
Lactose	102.15
Hydroxypropyl Cellulose	5.20
Crospovidone	6.50
Microcrystalline Cellulose	13.00
Magnesium Stearate	0.65
Subcoating	
Hydroxypropyl Methylcellulose	2.60
Coating	
Color Mixture White	5.30
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 5.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	5.00
Other Ingredients	
Lactose	156.00
Hydroxypropyl Cellulose	8.00
Crospovidone	10.00
Microcrystalline Cellulose	20.00
Magnesium Stearate	1.00
Subcoating	
Hydroxypropyl Methylcellulose	4.00
Coating	
Color Mixture White	8.16
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 7.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	7.50
Other Ingredients	
Lactose	234.00
Hydroxypropyl Cellulose	12.00
Crospovidone	15.00
Microcrystalline Cellulose	30.00
Magnesium Stearate	1.50
Subcoating	
Hydroxypropyl Methylcellulose	6.00
Coating	
Color Mixture White	12.24
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Olanzapine 10.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
Olanzapine	10.00
Other Ingredients	
Lactose	312.00
Hydroxypropyl Cellulose	16.00
Crospovidone	20.00
Microcrystalline Cellulose	40.00
Magnesium Stearate	2.00
Subcoating	
Hydroxypropyl Methylcellulose	8.00
Coating	
Color Mixture White	16.32
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

Claims

1. A solid oral formulation comprising olanzapine as an active ingredient intimately mixed with a bulking agent; binder, disintegrant, a dry binder to assure adequate friability, and a lubricant; wherein such solid oral formulation is coated with a polymer selected from the group cosisting of hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose.

2. A formulation as claimed by **Claim 1** wherein the polymer coat is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropylcellulose, methylcellulose, and ethylcellulose

3. A formulation as claimed by **Claim 2** wherein the polymer coat is hydroxypropylmethyl cellulose.

4. A formulation as claimed by any one of Claims 1 to 3 wherein the polymer coat is free of propylene glycol.

5. A formulation as claimed by **Claim 4** wherein the bulking agent is lactose.

6. A formulation as claimed by **Claim 4** wherein the binder is hydroxypropyl cellulose and the disintegrant is crospovidone.

7. A formulation as claimed by any one of Claims 1 to 6 wherein the dry binder is microcrystalline cellulose.

8. A formulation as claimed by any one of Claims 1 to 7 wherein the lubricant is magnesium stearate.

9. A formulation as claimed by any one of Claims 1 to 8 wherein the hydroxypropyl methylcellulose is a subcoating which is further coated with a aqueous dispersion film coat.

10. A formulation as claimed by Claim 9 wherein the solid formulation is imprinted using an edible ink.

11. A formulation as claimed by Claim 9 wherein the formulation comprises from about 1 to about 3 % w/w olanzapine; from about 69.5 to about 87.5 % w/w lactose; from about 3.5 to about 4.5 % w/w hydroxypropyl cellulose; from about 4 to about 6 % w/w crospovidone; from about 9 to about 11 % w/w microcrystalline cellulose; and from about 0.25 to about 1 % magnesium stearate.

12. A formulation as claimed by any one of Claims 1 to 11 wherein the solid formulation is a tablet.

13. A formulation as claimed by Claim 12 wherein each tablet provides a dose of olanzapine selected from the group consisting of 1, 2.5, 5, 7.5, 10, 15, and 20 mg.

14. A formulation as claimed by any one of Claims 1 to 13 wherein olanzapine is substantially pure Form II polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d (A)
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366

3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

15. A process for preparing a stable pharmaceutically elegant solid oral formulation containing olanzapineas an active ingredient and having a polymer coating selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose, comprising high shear aqueous wet granulation with fluid bed drying.

16. A process as claimed by Claim 15 wherein olanzapine is substantially pure Form II polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d (A)
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158

4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

17. A solid formulation as claimed by any one of Claims 1 to 14 for use in treating a condition selected from the group consisting of psychosis, schizophrenia, a schizophriform disorder, mild anxiety, a gastrointestinal disorder, and acute mania.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/03918

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/32, 9/36
US CL :424/464, 474, 475, 479, 480, 482

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 474, 475, 479, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,172,831 A (CHAKRABARTI ET AL.) 30 October 1979, example 37.	1, 12
A	US 5,229,382 A (CHAKRABARTI ET AL.) 20 July 1993, example 4.	1, 12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 JUNE 1996	09 JUL 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-2351

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